Solid Organ Transplantation in Sarcoidosis

J. Yserbyt, MD, PhD[1,2] W. A. Wuyts, MD, PhD[1,2] S. E. Verleden, MSc, PhD[1,2]
G. M. Verleden, MD, PhD[1,2] D. E. Van Raemdonck, MD, PhD[3] E. K. Verbeken, MD, PhD[4]
B. M. Vanaudenaerde, MSc, PhD[1,2] R. Vos, MD, PhD[1,2]

[1] Department of Clinical and Experimental Medicine, Lab of Respiratory Diseases, Lung Transplantation Unit, KU Leuven, Leuven, Belgium
[2] Department of Respiratory Medicine, Lung Transplant and Respiratory Intermediate Care Unit, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[3] Department of Experimental Thoracic Surgery, Department of Thoracic Surgery, KU Leuven and University Hospitals Leuven, Leuven, Belgium
[4] Department of Histopathology, KU Leuven, Leuven, Belgium

Address for correspondence Robin Vos, MD, PhD, Division of Clinical and Experimental Medicine, Laboratory of Respiratory Diseases, Lung Transplantation Unit, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium (e-mail: robin.vos@uzleuven.be).

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Abstract

Sarcoidosis is a chronic systemic inflammatory disease which is histopathologically characterized by the presence of noncaseating granulomas. When the extent of the disease is limited, without endangering the function of affected organs, clinical observation can be sufficient given that in a majority of cases, inflammation will subside with time. In more advanced sarcoidosis, especially when one or more specific organs are threatened, immunomodulatory treatment, of which steroids are the key element, over a prolonged period of time, in general, may attenuate disease activity. Treatment-refractory sarcoidosis (due to the lack of efficacy, drug toxicity or intolerability) may be progressive and, although infrequent, can result in end-stage organ failure. In these selected cases, solid organ transplantation (SOT) should be considered. In this article, SOT is positioned within the organ-specific treatment of systemic sarcoidosis and data on outcome after transplantation are discussed.

Keywords
- heart transplantation
- kidney transplantation
- lung transplantation
- orthotopic liver transplantation
- sarcoidosis
- outcome

Sarcoidosis is an inflammatory disorder of unknown etiology, diagnosed by the presence of noncaseating granulomas on histopathological examination. The disease involves the respiratory system in more than 90% of cases. The most frequent extrapulmonary manifestations are the eyes, lymph nodes, joints, and the skin, although essentially any organ system can be involved.[1]

Who and when to treat, as well as duration of treatment are the most compelling clinical conundrums. Systemic corticosteroids are generally acknowledged as first-line treatment of systemic sarcoidosis, although the scientific evidence for this approach is scarce.[2] Although potentially treatable in a vast majority of patients, sarcoidosis activity may linger in some cases under corticosteroids necessitating a longer and persisting course of treatment using a combination of steroids and so-called steroid-sparing drugs or "disease modifiers" in some cases.[3] Partial or complete treatment refractoriness and drug toxicity are the most important limiting factors in the success of pharmacological treatment of sarcoidosis. Although remission occurs in about two-thirds of patients after prolonged treatment (1–2 years), the remaining patients will evolve toward chronic or even progressive disease.[4] Therefore, end-stage organ failure as a direct result of sarcoidosis and/or as a result of treatment toxicity is a valid indication for solid organ transplantation (SOT) in selected patients.

Lung Transplantation in Pulmonary Sarcoidosis

With a proportion of 2.5% of all worldwide referrals for lung transplantation (LTx) between 1995 and 2011, sarcoidosis can be considered a marginal stakeholder in this respect.[5] Nevertheless, some reports suggest an increase of referrals for LTx during recent years. The selection criteria for referral

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and listing of sarcoidosis patients for LTx are comparable to what has been put forward for other end-stage fibrotic lung disease (e.g., idiopathic pulmonary fibrosis [IPF]).[6] The International Society for Heart and Lung Transplantation recently updated the disease-specific referral criteria for LTx, stating that for fibrotic lung disease (including sarcoidosis), New York Heart Association functional Class III or IV, or any of the following factors are critical: hypoxemia at rest, hypoxemia during exercise, pulmonary hypertension (systolic pulmonary arterial pressure [PAP] > 35 mm Hg on echocardiography, or mean PAP > 25 mm Hg on right heart catheterization, or elevated right atrial pressure > 15 mm Hg), forced vital capacity < 80% predicted, or diffusion capacity < 40% predicted.[5–7] Progressive pulmonary fibrosis, recurrent respiratory infection, and pulmonary hypertension are the leading contributors to respiratory failure and as a result important causes of mortality in pulmonary sarcoidosis. Severe and progressive pulmonary sarcoidosis, which in clinical practice equals progressive fibrotic disease warrants prompt referral for possible LTx.[7] Moreover, waiting list mortality in patients with fibrotic, restrictive lung disease is the highest among all indications for transplantation, and may increase up to 25 to 30% with increasing time spent on the waiting list.[8] Therefore, timely referral for transplant evaluation is crucial in these patients.[5–7] In clinical practice, however, timely referral for transplantation is not always so obvious. On the contrary, quantitative models predicting mortality in sarcoidosis are lacking and lung functional parameters do not always reflect clinical behavior of the disease.[9] Therefore, rules of thumb to guide clinical decision making and assessing disease severity are nonexistent. Referral for LTx should therefore be assessed on a case-by-case basis, considering the patient as a whole and looking for criteria of end-stage or refractory disease. Single-sided or unilateral LTx might still be a valid choice for selected sarcoidosis patients, in whom the burden of immunosuppression-triggered respiratory tumors in the remaining native lung plays a less important role compared with IPF. The choice for single LTx is taken based on local institutional factors such as donor organ availability and waiting list mortality.[8] Nevertheless, infectious complications of fibrotic pulmonary sarcoidosis, such as recurrent suppurative infections, bronchiectasis, or chronic mold infections, as well as better long-term survival in bilateral versus single LTx have nowadays prompted many centers to perform bilateral LTx instead of single LTx in fibrotic pulmonary disease.[7,8]

Early outcome after LTx might be disadvantageous for sarcoidosis patients. A 2014 meta-analysis of 13 studies involving a total number of 10,042 LTx recipients and comprising 98 cases of sarcoidosis stated that sarcoidosis as indication for LTx leads to a 50% prevalence of primary graft dysfunction (PGD) and was shown to be an independent risk factor for PGD (odds ratio: 4.25, 95% confidence interval: 1.09–16.52) using chronic obstructive pulmonary disease as benchmark and irrespective of lung transplant type (single or bilateral).[10] End-stage fibrotic disease such as sarcoidosis is associated with more difficult surgical pleural dissections and thus a higher risk of postoperative hemothorax.[11,12] Indeed, an increased incidence of hemothorax up to 25% has been reported in sarcoidosis, resulting in decreased ventilator-free days, increased length of stay on intensive care unit, and increased hospital length of stay after LTx.[12] Even though sarcoidosis is an independent predictor of early mortality as a result of an increase in PGD among these patients,[12] many reports conclude that long-term outcomes after LTx for sarcoidosis are similar to other lung diseases.[13–15] Therefore, end-stage pulmonary disease due to sarcoidosis indeed is a justified indication for LTx, given the achievable survival benefit for appropriately selected patients with high risk of short-term mortality.[16] The largest cohort in the literature reports on 695 cases of LTx for sarcoidosis out of a total of 20,896 LTx recipients (3.3%) over a 25-year time period.[17] These authors show that sarcoid LTx recipients have similar median survival rates compared with the nonsarcoid LTx recipients. Regression analysis did not identify sarcoidosis as an independent factor for survival after LTx. Moreover, sarcoid LTx recipients did not have higher incidences of bronchiolitis obliterans syndrome (BOS), recurrent hypoxemia after LTx, and seemed to have lower rates of redo LTx, despite the fact that sarcoid can recur after LTx. Another report endorses the observation that BOS is not more common in sarcoid LTx recipients than in others.[18]

Posttransplant recurrence of noncaseating granulomas in lung allografts despite continuing immune suppression has been reported in up to 35% of cases; however, these findings usually are not clinically relevant (illustrated in ►**Fig. 1**).[19] These recurrent granulomas are originating from the recipient, as proven by the presence of donor/recipient chimerism on lung biopsies.[20] A Danish article describes a post-LTx sarcoid granuloma recurrence rate of 30%, interestingly, all cases of disease recurrence were documented by histopathological detection during surveillance bronchoscopies, without any clinical or radiological signs of sarcoid disease. Recurrent granulomas had no lung functional consequences and did not affect overall survival.[21] These findings were corroborated by a study of the Cleveland Clinic, reporting on 30 LTx procedures for sarcoidosis. Histopathological recurrence of noncaseating granulomas was noted in seven patients (23%) and was histologically detected on surveillance bronchoscopy in all patients. Only one out of these seven patients had radiological abnormalities compatible with pulmonary sarcoidosis, and sarcoidosis recurrence did not impact on post-LTx survival rates.[22] The observation that most recurrent cases are subclinical was confirmed by another report stating that in only one out of three cases of recurrent pulmonary sarcoidosis, radiological changes are apparent (a posteriori assessment).[19] One article reports on a case of sarcoid recurrence after single LTx, necessitating redo LTx with eventually again sarcoid recurrence in the second lung allograft in the same patient.[23] This again highlights the benefit of performing bilateral LTx (which implies more lung functional "reserve" in case of disease recurrence) instead of single LTx. Nevertheless, long-term outcome may still be compromised in some of these patients in case of progressive disease after post-LTx sarcoid recurrence, as is illustrated in a case from the current authors' center (►**Fig. 2**).

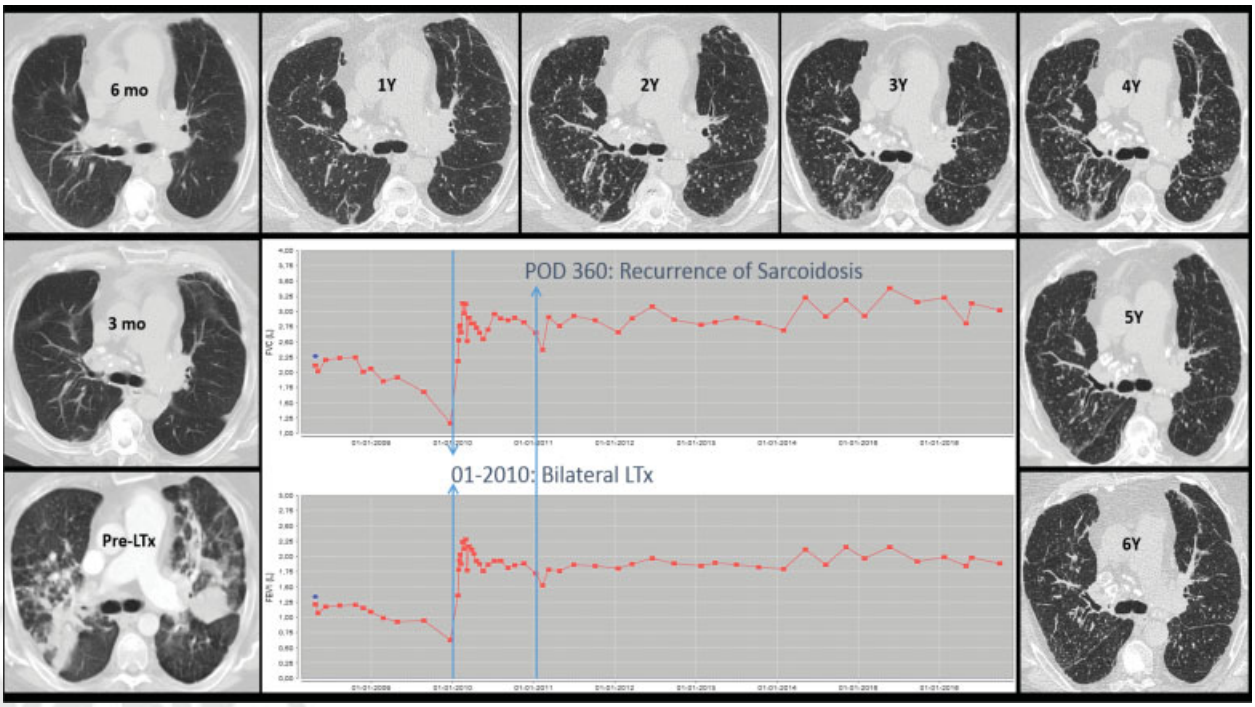

Fig. 1 Recurrence of sarcoidosis with stable pulmonary function after bilateral lung transplantation in a 41-year-old man. Evolution of radiology (consecutive chest CTs pretransplant, at 3, 6 months, and 1–6 years posttransplant) and of pulmonary function (forced vital capacity, L, top and forced expiratory volume in 1 second, L, bottom) over time after bilateral LTx for sarcoidosis in a 41-year-old man. Recurrence of sarcoidosis, despite maintenance treatment with methylprednisolone, cyclosporine (later tacrolimus), and azathioprine was diagnosed on POD 360 by means of CT, demonstrating micronodules in upper lobes and transbronchial biopsies, demonstrating the presence of noncaseating granulomas. Over time after transplantation bilateral pleural thickening, diffuse centrilobular, and fissural micronodules (i.e., typical perilymphatic distribution) were evident, despite which pulmonary function remained stable. CT, computed tomography; Ltx, lung transplantation; POD, postoperative day.

Extrapulmonary Sarcoidosis

A multicenter case–control study on clinical characteristics of sarcoidosis in the United States (A Case Control Etiologic Study of Sarcoidosis) showed that half of all 736 sarcoidosis patients included in the study had both pulmonary and coexisting extrapulmonary sarcoidoses.[24] Only 2% of all study subjects were characterized with isolated extrapulmonary disease. Although some have questioned whether the studied cohort was representative for the general patient population, these proportions are far above what is estimated based on clinical expertise, showing that the search for extrapulmonary sarcoidosis needs to be addressed more thoroughly. Extrapulmonary disease manifestations may lead to significant morbidity and should therefore be addressed early in the course of the disease, although subclinical findings in nonvital organ systems may not lead to therapeutic consequences. Renal, cardiac, and hepatic sarcoidoses are discussed separately with an emphasis on the positioning and the outcome of transplantation for these indications. Estimated frequencies of extrapulmonary organ involvement are summarized in ►**Fig. 3**.

Renal Disease and Kidney Transplantation in Sarcoidosis

Renal involvement in sarcoidosis can be the result of different pathophysiological mechanisms, which can act both independently or in combination. Granulomatous lesions may produce calcitriol leading to an increased urinary excretion of calcium. Hypercalciuria occurs in about half of sarcoidosis patients and generally precedes development of hypercalcemia, which occurs in ~10% of cases of sarcoidosis, whenever serum calcium is abundantly higher than the excretion potential of the kidney. Hypercalciuria and hypercalcemia as such may progress to renal insufficiency.[25] Tubulointerstitial nephritis can occur as a direct consequence of systemic sarcoidosis. Histological findings are often not specific for sarcoidosis because these cases of nephritis may be characterized by the absence of granulomas. Therefore, infection and drug hypersensitivity should be clinically excluded, as these are more frequent causes of interstitial nephritis. The exact prevalence of interstitial nephritis in the context of sarcoidosis is not well known. A single-center, retrospective study on more than 10,000 kidney biopsies revealed a definite histopathological diagnosis (noncaseating granulomatous interstitial nephritis) in 0.18%. In a subgroup of patients diagnosed with sarcoidosis prior to kidney biopsy, this number increased to 37%.[26] A third pathway to renal injury in sarcoidosis is nephrocalcinosis and/or nephrolithiasis, occurring as a result of hypercalcemia. An article on histopathology of kidney biopsy in sarcoidosis patients reports on 19 patients with noncaseating granulomatous interstitial nephritis, of whom 7 presented with hypercalcemia, but only 3 had evidence of microcalcifications.[26] Moreover, other renal disease such

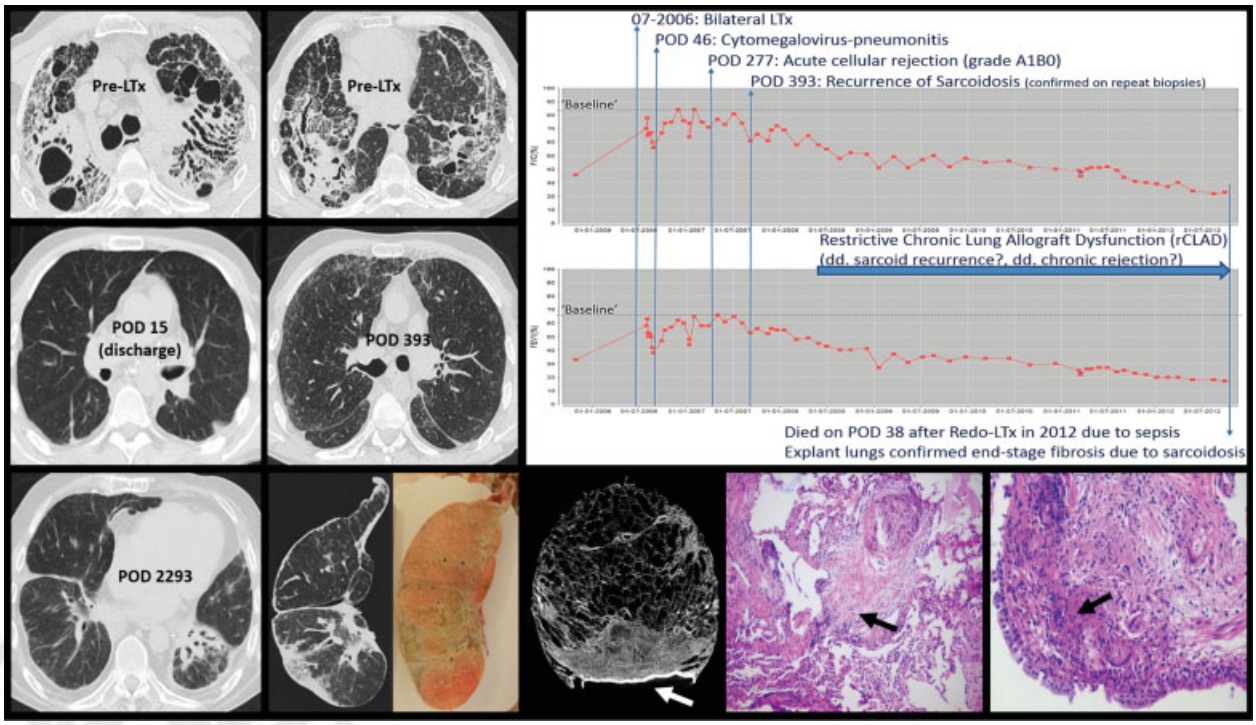

Fig. 2 Recurrence of sarcoidosis with decline of pulmonary function after bilateral lung transplantation in a 40-year-old man. Evolution of radiology (consecutive chest CTs, left panel) and of pulmonary function (right panel, forced vital capacity, %predicted, top and forced expiratory volume in 1 second, %predicted, bottom) over time after bilateral LTx for sarcoidosis in a 40-year-old man. Recurrence of sarcoidosis was diagnosed on POD 393 by means of transbronchial biopsies demonstrating the presence of noncaseating granulomas. Thereafter, despite maintenance treatment with prednisone, tacrolimus, and mycophenolate, pulmonary function progressively worsened over the subsequent 5 years due to progressive pulmonary fibrosis, resulting in restrictive CLAD with respiratory insufficiency. Chest CT on POD 2,993, shortly before redo transplantation, demonstrates marked bilateral pleural and fissural thickening, as well as subpleural consolidation. Shortly after redo transplantation, the patient unfortunately succumbed due to postoperative sepsis. Explant lungs (demonstrated in the insets of the right explanted lung, showing ex vivo CT and gross histology) demonstrated significant fibrosis with lymphatic spread, involving intralobular septae and visceral pleura. (Sub)pleural fibrosis (white arrow) is demonstrated in detail on micro-CT of a core biopsy of this explant lung. The presence of noncaseating granulomas (black arrows) is illustrated on histology of transbronchial and endobronchial biopsies at POD 393 (hematoxylin and eosin stain, ×100 left and ×200 right). CLAD, chronic lung allograft dysfunction; CT, computed tomography; Ltx, lung transplantation; POD, postoperative day.

as immunoglobulin A nephropathy coexisting with one of the renal conditions mentioned earlier is not uncommon.[27] Hydronephrosis as a result of retroperitoneal infiltration or inflammation and as a result of mechanical compression (e.g., lymphadenopathy) are theoretically also possible, but infrequently reported.[26–28] Patients with sarcoidosis may well be affected by renal insufficiency, but diabetic or vascular nephropathy is more likely in these cases than sarcoid-induced renal insufficiency. Sarcoidosis-related end-stage renal disease is an exception in clinical practice, although a significant degree of renal insufficiency with evidence of hypercalcemia as a contributing factor has been reported in a retrospective series.[28] Both sarcoid-related interstitial nephritis and hypercalcemia respond well to treatment with systemic steroids in combination with auxiliary measures for calcium control (avoidance of exogenous calcium/vitamin D, diuretics, bisphosphonates). Adjunctive treatment with ketoconazole, hydroxychloroquine, azathioprine, or mycophenolate mofetil have rarely been reported in cases of granulomatous interstitial nephritis unresponsive to systemic steroids.[29] In conclusion, end-stage renal disease as a direct result of sarcoid nephritis is rare but can be an indication for kidney transplantation (KTx) in very selected cases in which pharmacological treatment fails.

Outcome of KTx in the context of sarcoidosis-related renal insufficiency is comparable to overall outcomes after KTx for other indications. Nevertheless, reactivation of known sarcoidosis has been described in the setting of KTx.[30] In the previously mentioned retrospective report on kidney histopathology,[26] a total of 2,331 kidney biopsies from renal grafts were assessed, among which two were obtained from grafts of patients who underwent KTx because of biopsy-proven renal sarcoidosis. One of these patients was found to have recurrence of granulomas on posttransplant kidney biopsy (without infections or nephrotoxic drugs), although without any signs of renal graft failure. The most detailed examples of recurrence after KTx were reviewed in a case series of 18 patients who underwent KTx with a previous diagnosis of sarcoidosis. In five patients (27%) who had disease recurrence, two developed renal sarcoidosis and three had extrarenal manifestations, a mean period of 13 months following

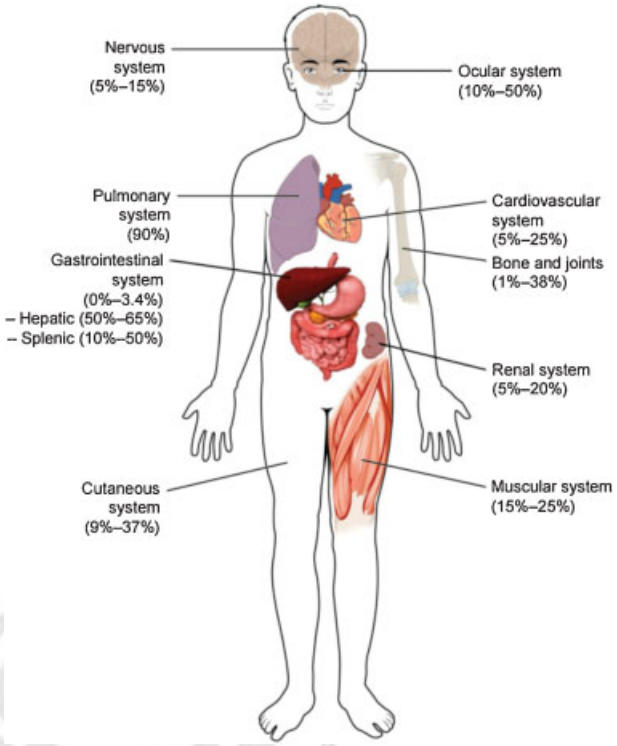

Fig. 3 Estimated frequencies of organ involvement in sarcoidosis. (Modified from OpenStax College, Anatomy and Physiology. OpenStax CNX. Available at: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@8.24. Permission for publication granted by Dove Medical Press Ltd.)

KTx. All patients were receiving immunosuppression (including low-dose prednisolone) at the time. Guided by these observation, sarcoidosis relapse may occur in up to a quarter of patients after KTx and may negatively impact on renal graft survival.[31]

Cardiac Disease and Heart Transplantation in Sarcoidosis

Exact prevalence of cardiac sarcoidosis is hard to balance between clinical reporting and data from autopsy studies. In general, cardiac involvement is clinically estimated at 5% in sarcoidosis patients,[32] although autopsy studies reveal a much higher prevalence of 25% and above.[33] Therefore, it is quite conceivable to assume a high rate of subclinical involvement, making overt cardiac sarcoidosis a rather rare manifestation. Even in the presence of cardiac failure, a correct diagnosis of cardiac sarcoidosis is often hard to achieve. This is demonstrated by a report on histopathologic examination of 314 explanted hearts, revealing only 8 cases (2.5%) of cardiac sarcoidosis, none of which was diagnosed prior to transplantation.[34] On the contrary, cardiac sarcoidosis is a potential lethal disorder with low survival rates if left untreated. Endocardial, myocardial, and pericardial abnormalities may be present on histology. Cardiac sarcoidosis may present as atrioventricular or intraventricular heart block, ventricular tachycardia, (un)sustained ventricular fibrillation, cardiomyopathy, or in the most dramatic cases sudden death.[33,35] Progressive heart failure due to granulomatous infiltration of the myocardium is the main cause of death in cardiac sarcoidosis. Overall mortality in sarcoidosis is attributable to cardiac involvement in 13 to 85%, depending on ethnicity.[35] In addition to specific cardiologic therapies (antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, β-blockers, implantation of pacemaker or implantable cardiac defibrillator), treatment of cardiac sarcoidosis consists out of systemic steroids, although evidence for dosing, timing, and outcome of steroid treatment is again lacking. Some reports suggest a better outcome of left ventricular function when methotrexate is added to steroid treatment.[36]

Data on overall, long-term, transplantation-free survival in patients with cardiac sarcoidosis are very heterogeneous due to historic, ethnic, and methodological reasons. Articles in the late 1970s and 1980s of cardiac sarcoidosis reported disappointingly low survival of 27% 1 year after symptom onset[37] and 40% 5-year survival, respectively.[38] In a recent multicenter Japanese study, 5-year survival was 60 to 75%[39] and another multicenter study of the early 2000s reported transplantation-free 5-year survival rates of 60 to 70%.[40] In contrast, smaller studies in the same era reported a 5-year survival exceeding 90%.[41–43] Recently, 1-, 5-, and 10-year transplantation-free cardiac survival rates of 97, 90, and 83% were reported, respectively.[32] Prospective data on the outcome of cardiac sarcoidosis are even more rare. Smaller studies looked at correlation of late gadolinium enhancement on cardiac imaging (magnetic resonance imaging [MRI]) and found cardiac mortality rates of 8 to 19% in this specific subset of patients.[44,45] These findings, however, seem less consistent to reproduce since a prior 2008 study demonstrated no mortality whatsoever in patients with cardiac symptoms or radiologic (positron emission tomography/MRI) features indicative of cardiac sarcoidosis during a 2-year follow-up.[46] Nevertheless, given the possible life-threatening consequences, physicians should always have a high index of clinical suspicion for possible cardiac involvement in patients with sarcoidosis.

Similar to other causes of end-stage cardiac disease, heart transplantation (HTx) should be considered in sarcoid-induced heart failure when all other therapies have failed.[47] Most reports on sarcoidosis and HTx are largely based on transplantation of patients with "idiopathic" cardiac failure (i.e., without clinical diagnosis of sarcoidosis prior to transplantation), in whom sarcoidosis was detected histopathologically on the explanted heart.[48] Therefore, clinical practice should be interpreted in this given context. Overall, cardiac sarcoidosis as indication for HTx remains a rarity among HTx recipients, with proportional estimates of 1.3 to 1.8%.[48,49] Only 33 to 42% of these patients had a histology-endorsed pretransplant diagnosis of extracardiac sarcoidosis and only 21% had biopsy-proven cardiac sarcoidosis.[48,49] Interestingly, some authors report an increasing number of cases of cardiac sarcoidosis in patients listed for HTx during the past decades. Al-Kindi and Oliveira identified a total of 150 adult patients with cardiac sarcoidosis listed for HTx

between 1994 and 2014. During this period, a fivefold increase in the proportion of sarcoid cases with heart failure requiring HTx was seen: 0.1% (1994–1997) to 0.5% (2010–2014). The proportion of cardiac sarcoidosis among cases of restrictive cardiomyopathy increased in parallel from 5 to more than 15% during the same era.[50] As one would expect due to increased awareness and better screening methods, similar findings on increased detection rate of cardiac sarcoidosis were reported: a more than 20-fold increase of the annual detection rate of cardiac sarcoidosis was seen between 1988 and 2012 in a Finnish Nationwide Study.[32,50]

Overall survival after HTx for sarcoidosis is reported to be comparable to other indications for HTx: 86% at 1 year, 84% at 5 years, and 58% at 10 years.[50] Comparable overall survival rates are reported by other authors: 92% at 1 year and 83% at 5 years in a recent study in the United Kingdom.[48] Kandolin et al report on 11 cases of HTx, out of a pool of 110 patients followed up between 1988 and 2012, in whom 1-year, 3-year and 5-year survival rates were 82, 73, and 64%, respectively.[32] Perkel et al report a 5-year posttransplant survival of 79%, a 1-year freedom from any treated rejection of 79%, a 5-year freedom from cardiac allograft vasculopathy of 68%, and a 5-year freedom from nonfatal major adverse cardiac events of 90%. All these rates were comparable to what was found in a contemporary control group of nonsarcoid heart and LTx recipients.[49] Recurrence of sarcoidosis in the allograft has been reported when tapering steroids[51–53] but seems to be rare, since no cases of recurrent cardiac sarcoidosis and limited progression (0–19%) of concurrent extracardiac sarcoidosis were described in some larger cohorts during a total follow-up time of more than 20 years.[48] Some state that maintaining sarcoidosis patients on low doses of corticosteroids after HTx may prevent sarcoid recurrence in the allograft.[51] As a result, potential disease recurrence should not be considered a reason to withhold HTx from patients with end-stage heart failure due to cardiac sarcoidosis.[49]

Hepatic Disease and Liver Transplantation in Sarcoidosis

Clinically, overt hepatic disease as a result of sarcoidosis is very rare, although noncaseating granulomas of the liver are present in up to 65% of patients with systemic sarcoidosis[54] and postmortem studies demonstrated that hepatic granulomas are present in ~80% of patients with sarcoidosis.[55] Clinically, hepatic sarcoidosis should be suspected when patients with systemic sarcoidosis present with hepatomegaly, right-sided hypochondric pain, elevated serum liver function tests, and/or nodular changes of the liver parenchyma on ultrasound or computed tomography scan. When histologic confirmation is needed (e.g., to guide treatment decisions), liver biopsy should be pursued. Systemic corticoids can be effective in reducing liver size, resulting in symptomatic relief, although its effects on number of granulomas and liver function are less convincing.[56] Corticosteroids are less useful in changing the disease course and evidence-based data that steroid treatment may reduce portal hypertension or hepatic fibrosis are disappointing.[56] Steroid-sparing agents have been used with some success. Azathioprine is preferred over methotrexate by some, although both are potentially hepatotoxic.[2,3] Chronic, persistent hepatic inflammation in the context of sarcoidosis may lead to portal hypertension in 3 to 18% of patients, potentially causing variceal bleeding.[57] Compression of portal venules by intrahepatic granulomas is a possible mechanistic explanation for this observation. Only a small proportion of patients with sarcoid liver disease (6–8%) develop secondary portal hypertension following prior progression to cirrhosis.[58]

In end-stage sarcoid liver disease, orthotopic liver transplantation (OLTx) has been successfully used as a treatment modality. Cases of sarcoidosis-induced end-stage liver disease account for ~0.012% of the total number of liver transplantation in the United States.[59] Since clinically overt hepatic disease is infrequent and OLTx is only performed in a fraction of patients with end-stage liver disease, data on outcome of OLTx in sarcoidosis are even rarer compared with other SOT for sarcoidosis. A recent multicenter article reports on 13 cases of OLT in sarcoidosis, comprising 1.3% of all OLT cases. Long-term outcomes were described in a case–control method, showing that 1-, 3-, and 5-year survival rates after OLTx did not differ between sarcoidosis patients and a matched group of patients with primary sclerosing cholangitis or primary biliary cirrhosis.[60] This contrasts with earlier observational findings of the same group reporting that outcome after OLTx could be impaired for sarcoidosis patients compared with primary sclerosing cholangitis or primary biliary cirrhosis (5-year graft-survival rates of 60 vs. 75%). The authors speculate that hepatic sarcoidosis reflects systemic sarcoidosis, which may lead to impaired fitness of the patient before or after OLTx as a result of extrahepatic disease.[61] The observation that outcome of OLTx for sarcoidosis is comparable to what is seen for other OLTx indications has been confirmed by others showing allograft-survival rates to be comparable with other cholestatic and parenchyma liver diseases (86% after 5 years).[62] Recurrences of granulomatous inflammation may occur in the hepatic allograft and seem to be controllable with increased doses of systemic corticosteroids.[63] Bilal et al show recurrence of hepatic sarcoidosis in 4 out of 13 patients (31%) at 11, 112, 222 days, and 6.6 years post-OLTx, respectively.[60]

Conclusion

Selection of sarcoidosis patients for organ transplantation should be performed in a holistic approach, assessing the potential success and side effects of immunosuppressive therapies and the presence of extrapulmonary involvement (e.g., neurosarcoidosis) precluding transplantation. In the detrimental case of severe combined organ involvement, combined organ transplantation (e.g., heart–lung, heart–liver, lung–liver, and lung–kidney transplantation) could be considered, as is done for other (nonsarcoidosis) transplant indications. Sarcoidosis may recur after organ

transplantation, but the reports discussed in this article demonstrate that sarcoid recurrence is generally treatable with increasing systemic corticosteroids and overall does not lead to premature graft failure, except maybe for a minority of recurrent cases, especially after KTx. Posttransplant recurrence of sarcoidosis should therefore not be overestimated. This may be best illustrated by data in LTx describing incidental findings of noncaseating granulomas during posttransplant surveillance bronchoscopy. Given that sensitivity of transbronchial biopsies for diagnosis of parenchymal lung disease in sarcoidosis is only 30 to 70%, one may assume that the actual incidence of disease recurrence after LTx is probably underestimated. Nevertheless, long-term posttransplant outcomes in these cases are overall excellent and comparable to nonsarcoid LTx recipients. The main reason why recurrent disease after SOT can be considered "clinically irrelevant granulomatosis" is probably the life-long immunosuppressive treatment of SOT recipients, allowing sufficient disease control and preventing further evolution to fibrosis in most patients. As a result, possible posttransplant recurrence of sarcoidosis should be no reason to withhold transplantation from otherwise eligible patients suffering from end-stage organ failure due to sarcoidosis. In general, SOT for sarcoidosis has good long-term outcomes and may result in significant survival benefit for appropriately selected patients with high risk of short-term mortality.

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